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Mediastinal Mass Revealed by Thyrotoxicosis Crisis. Be Aware of Thymic Hyperplasia. A Case Report

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ASTRACT

Introduction: Thymic hyperplasia (TH) is a rare condition that includes tumor-like syndrome of the upper mediastinum and GRAVE'S disease (GD). Chest discomfort, shortness of breath, upper chest pain associated with thyrotoxicosis symptoms can be misleading namely in an emergency setting.

Case Report: A 30-year-old female patient presented with sinusal tachycardia >100/min, and oppression thoracic signs. MDCT of the chest ruled out pulmonary embolism and disclosed a thymic mass, in a clinical context of GD.

Conclusions: Thyroid hormones and auto immunity play a crucial role in TH. General physicians should be aware of this association to avoid aggressive management, namely surgical intervention, along with its associated potential complications and costs.

Keywords: Thymic hyperplasia; Grave's disease; Autoimmune; Mediastinal mass; Thyrotoxicosis; Hyperthyroidism; Pulmonary embolism; Thyrotropin receptor antibodies Trab

INTRODUCTION

Grave's disease (GD) is an autoimmune disorder associating the development of antibodies directed against the thyrotropin receptor (TSH-r) [1]. The resulting thyroid enlargement is thus due to thyroid follicular cell hyperplasia and hypertrophy. Concomitantly, TSH-r antibodies (Trab) activation leads to overproduction of thyroid hormone synthesis and secretion, and subsequently hyperthyroid clinical state [2]. The thymus belongs to the immune system, and enlarges as T-cell mediated immune response develops, due to production of Trab by B-lymphocytes. The association between GD and thymic hyperplasia (TH) remains largely unrecognized in clinical daily practice, probably due to the limited chest MDCT evaluation in GD patients and lack of knowledge of the association among general practicioners.

CASE PRESENTATION

A 30years old female patient, 15 pack years of tobacco abuse, Body mass index (BMI) 31.7, no oral contraception, was transferred to the emergency department. Patient reported chest discomfort, shortness of breath, upper chest

pain, dyspnea, anxiety and palpitations. Clinical examination showed a bilateral lower limb edema. Blood pressure was 145/89mmHg, Heart rate: 105/min, respiratory rate 15/min. Homans sign was negative, there were no sign of pelvic compression [3]. D-dimer serum level was moderately elevated, Oxygen saturation was 98%, electrocardiogram was normal (sinusal tachycardia), Doppler ultrasound examination of the lower and upper limbs did not reveal any venous clot. MDCT of the pulmonary arteries ruled out diagnosis of acute pulmonary embolism. There was no image in favor of pulmonary infarction. However, MDCT disclosed a thymic bulging mass, presenting with convex regular margins in the upper anterior left mediastinum, 25 mm thick, close to the left innominate vein and the aortic arch (Figure 1 and 2). Its density was +50HU at portal phase examination, its largest axial surface was estimated around 350mm^2. There was no objective muscle weakness, no ptosis, no dysphagia. Patient had no history of myasthenia gravis, systemic lupus erythematous, scleroderma.

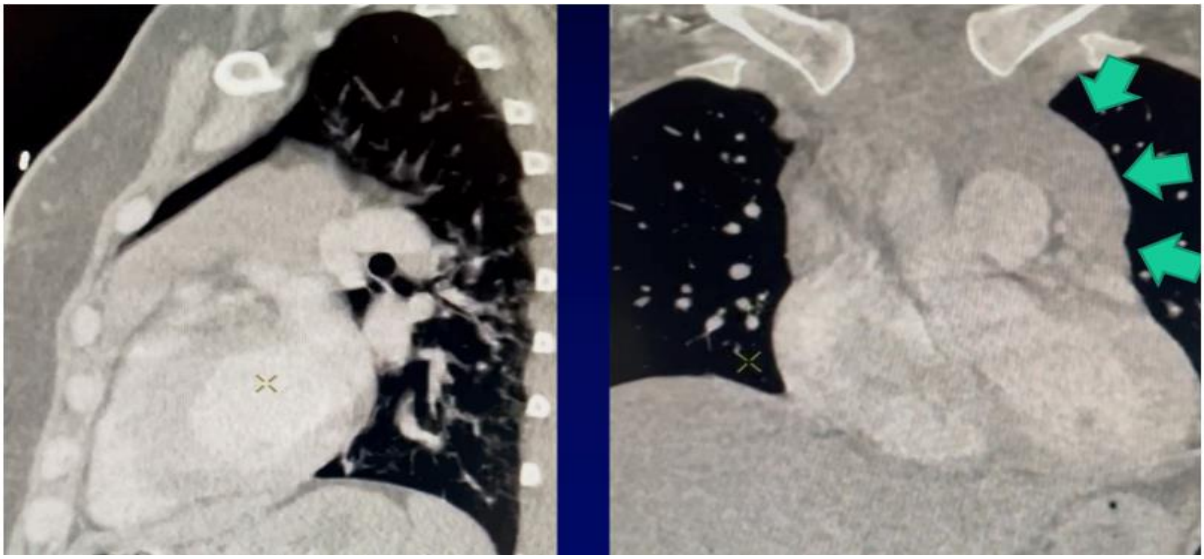

Figure 1: Thymic hyperplasia due to Grave's disease, at initial work up. Sagittal and coronal MDC reformations showing bulging (arrows) asymmetric anterior mediastinal mass. Such initial aspect was suspicious for thymoma.

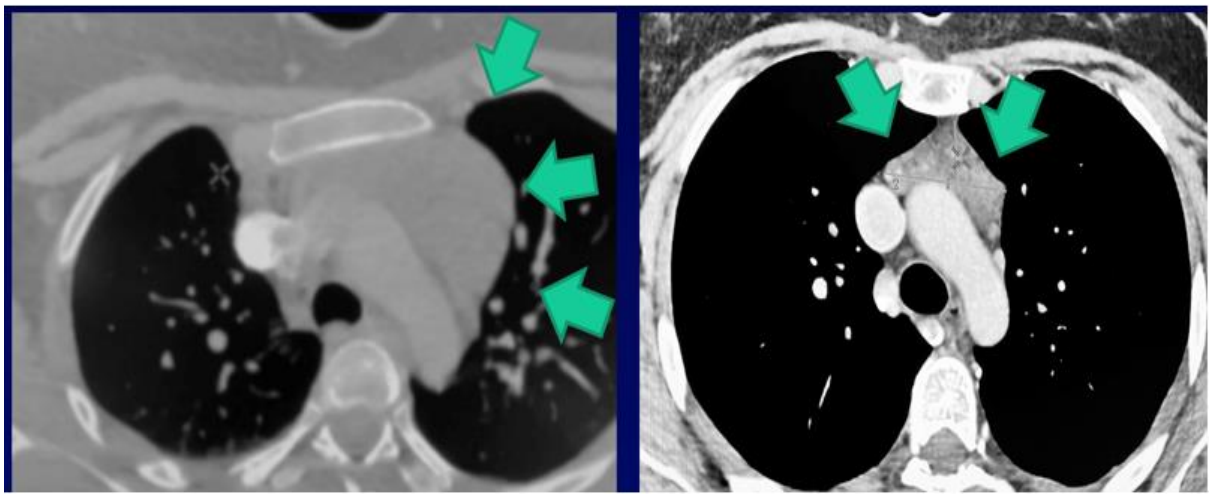

Figure 2: Thymic hyperplasia due to Grave's disease, at initial work up, and at nine months follow-up. Thymic attenuation and axial surface were respectively +50HU, and 350mm2 initially, and +10HU and 150mm^2 at nine months follow-up. Note the rounding convex edge of the bulging mass before Thiamazole initiation (arrows),

little mass effect on tracheal lumen. At nine months follow-up, 75% shrinkage of the TH is shown in a typical « benign » concave symmetrical bilobate shape (arrows). Thymic measurement should always be compared to the reported normal values in the corresponding age group, as size and volume typically change over time [6,10,14, 15].

Doppler US Doppler US disclosed a diffuse hypo echoic hyper vascular 33ml goiter (normal range: 6-18ml), systolic velocity peaks up to 150m/sec. There was neither internal jugular vein invasion nor suspicious neck / mediastinal lymphadenopathy. Thyroid scintigram showed a high diffuse glandular uptake (homogeneous uptake of 68.7% on iodine -123 scan, that was in favor of Grave's disease. Patient had no eye complaints, dysphagie, dysphonia, tremor, insomnia, or weight loss. Biological laboratory tests reported (TSH Thyroid Stimulating Hormone) TSH <0.01, T4 48.8 (normal < 22), thyroperoxidase antibodies TPOAb 520U/mL (normal < 34), Thyroid-stimulating hormone receptor antibodies TRAbs 12.8 IU/L (normal < 1.75). Patient was given Thiamazole 60mg/day and B blocker. Acetylcholinesterase antibodies (Ab) were negative.

At follow up, patient responded well to therapy; The thyroid function and thyroid-stimulating hormone TRAb) respectively normalized one and five months after Thiamazole initiation. The anterior superior mediastinal asymmetric convex mass showed significant volume reduction (350mm^2 to 150mm^2 = 75%), attenuation, and shape modifications (Figure 1B) at nine months' chest- CT follow-up, (Figure 2) and normal features at twelve months.

As patient presented with convex asymmetrical shape, MRI was performed and showed typical « benign » decreased signal on chemical shift sequences (Figure 3). Concomitantly, pretibial myxedema resolved and the patient is still free of disease at three years follow-up.

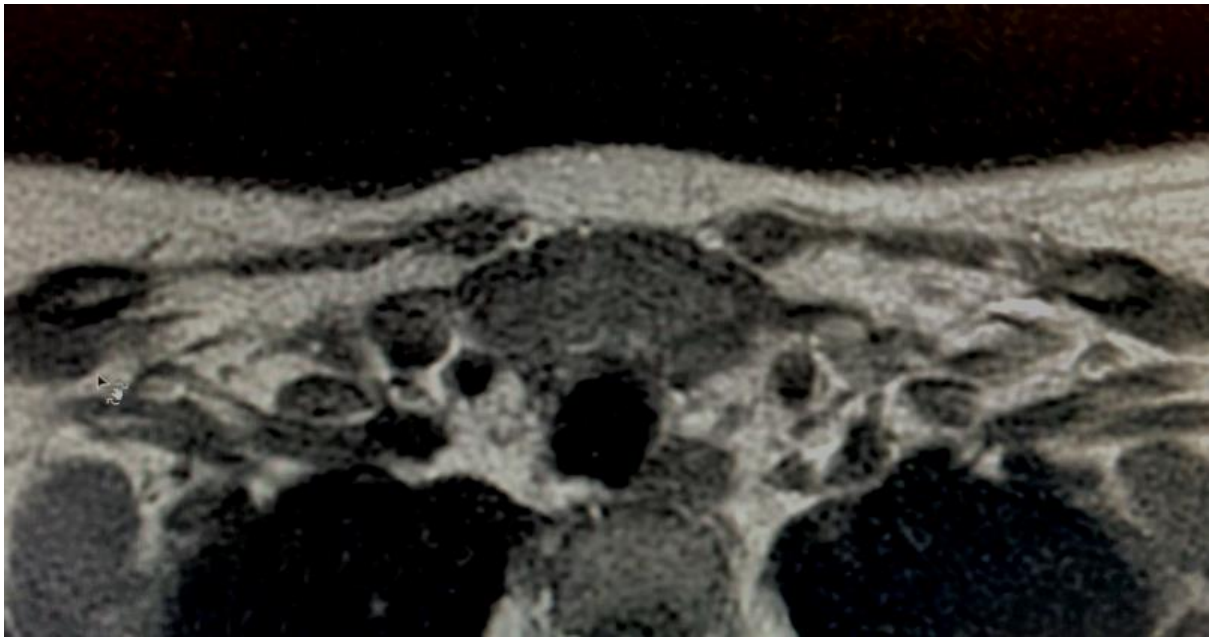

Figure 3: GD related TH, axial MRI feature at nine months' follow-up.

Chemical shift sequence shows dramatic drop (hypo intensity) of signal on upper part of thymus. Volume reduction and hypo signal were consistent with diagnosis of thymic benign hyperplasia [14,15].

DISCUSSION

The association between GD and TH has already been reported [4-6]. In the present case, Grave's thyrotoxicosis mimicked acute Pulmonary Embolism (PE); Pre-test probability score for PE was intermediate, as there were no cancer history, no cancer treatment in the previous 6months, no recent immobilisation > 3 days, no previous surgery, no previous venous thromboembolic events, no haemoptysis. Serum level of D-dimers, which are fragments of blood clot's protein released into the circulation of patient presenting with PE, was moderately elevated: 1600 µg/L) (normal <500 µg/L). Contrast enhanced thoracic MDCT ruled out PE, and showed strong suspicion for a thymic mass. Its MDCT attenuation was +50HU at portal phase examination, its largest axial surface was estimated around 350 mm^2. As clinical neural and biological (acetylcholine receptor antibodies were negative) examination ruled out a paraneoplastic syndrome potentially linked to myasthenia gravis [7], decision was made to follow the patient after three months of Thiamazole therapy, and MDCT at nine months.

Regarding bilateral lower limb edema, Doppler ultrasound formally ruled out venous clot; clinically, this was indeed the typical manifestation of myxoedema [8], which is a classical extrathyroidal manifestation of binding of the stimulatory autoantibodies (Trabs) to connective tissue cells such as subcutaneous fibroblasts. As the latter antigens look similar to those found in thyroid tissue, they may stimulate the synthesis of glycosaminoglycans and cytokines that promote fluid retention and local lymphedema. Myxoedema is a focal bilateral symmetrical thickening of the skin, without prurit or pain. Myxedema involves the pretibial area in more than 95% of the patients, very less often the upper limbs, neck, trunk, and ears, and should be seeked at initial work up of Grave 's disease (GD). As our patient did not have a previous diagnosis of thyroid disease and did not show symptoms of eye involvement, and clinical evidence of goiter, the initial diagnosis of Grave's thyrotoxicosis was uneasy. Emergency setting symptoms were quite misleading, and TSH serum level assessment was helpful to make the diagnosis.

Neck Doppler US is definitely useful in GD diagnosis and follow up [9]; it also can show the neck thymic hyperplasia (TH) and its dramatic reduction during treatment of Grave's disease [10]. TH may appear as a cervical mass located next the clavicular fossa with partial immersion in superior mediastinum. Typically, TH is trapezoidal shaped, and shows reduced echogenicity compared to the thyroid parenchyma, and a typical heterogeneous "marbled" echo pattern with no vascularity, as reported by Scappaticcio [10].

Murakami et al interestingly formally identified thyrotropin receptors in human thymus, thus explaining the physiopathological process of GD related TH. The authors also investigated the thymic size and CT attenuation of 23 patients with Graves disease, of whom were evaluated before and after treatment with anti-thyroid drugs for 5 to 24 months [11,13]. Mean thymic size decreased with age, from 220 to 143 mm^2 (from 20 years old to 59years old) and mean MDCT attenuation from -24HU to -83HU respectively, in control subjects. In GD patients, mean thymic size was 353 mm2 at 30-39years old patients and mean thymic MDCT attenuation was +34.5HU versus -38.6HU in control subjects. In the present case, our female patient presented initially with a GD 33.3ml hyper vascular « thyroid inferno» goiter, and 350mm2 thymic surface size, which is fully consistent with Murakami et al, and literature reports [5,6,10,12]. The relatively higher CT attenuation of TH in our patient, from 50HU (versus -24HU) initially to +1OHU (versus -83HU) nine months after Thiamazole is consistent with Araki et al, [13] who reported a threshold of 41HU optimal cut-off value for differentiating lymphoid hyperplasia from true hyperplasia. Indeed, thymic mass 's CT attenuation of +50HU in the present case was in favor of lymphoid hyperplasia of the

thymus. Other underlying autoimmune diseases including scleroderma, systemic lupus erythematosus, or myasthenia gravis should be seeked systematically (Table 1).

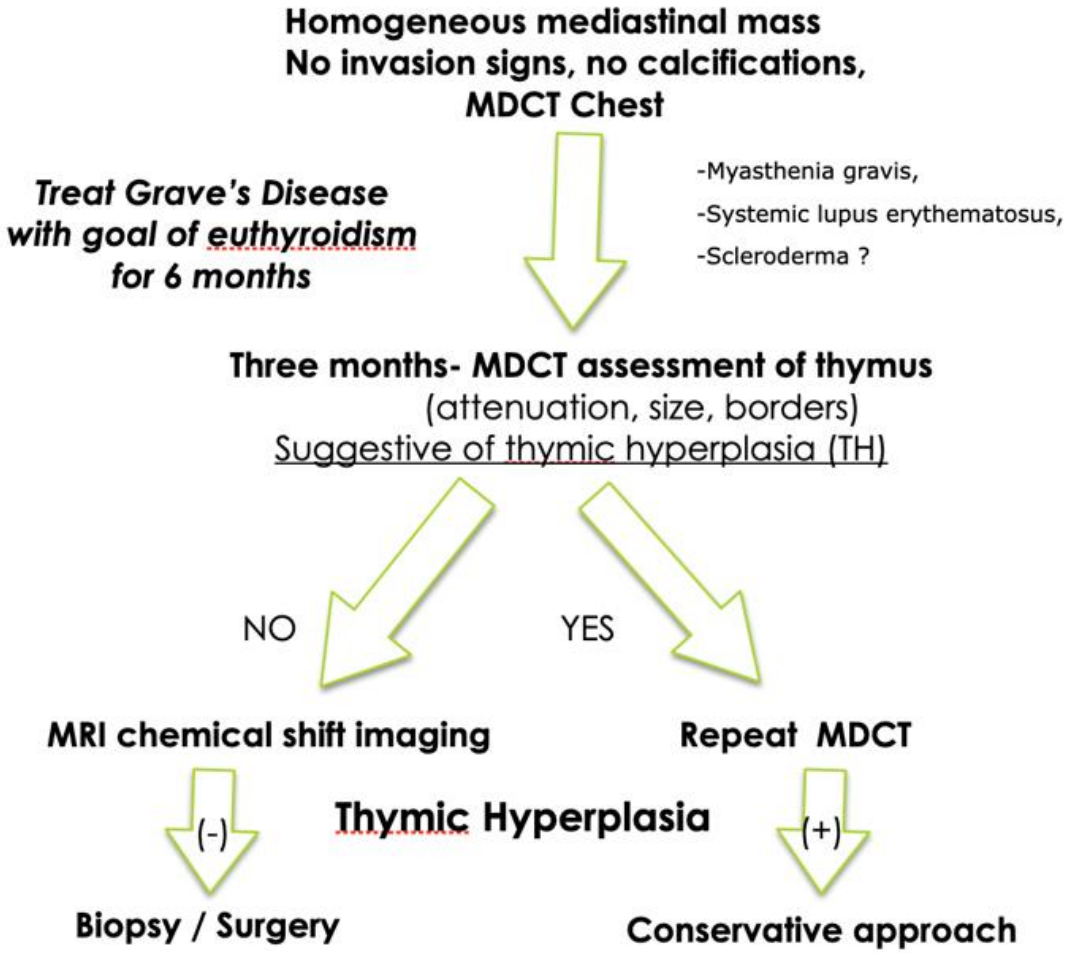

Table 1: Proposal for Imaging algorithm in case of suspicious GD related TH.

As we know, CT attenuation and volume of the thymus decrease with aging, and this should be kept mind when assessing the thymus gland on MDCT.

The decreased size of 145 mm^2 at nine months after Thiamazole initiation perfectly correlates with Murakami et al's reports of 143 mm^2 in control subjects and is fully consistent with complete regression of GD related thymic hyperplasia after therapy [11].

Regarding MRI assessment, TH appears as a mass with homogeneous appearance and regular contours throughout the various MRI sequences and a uniform loss of signal intensity on chemical shift MRI sequences. MRI definitely plays a key role in differentiating thymic hyperplasia from thymus gland tumors in adult patients > 16years old, as thymic tumors do not decrease their signal intensity on chemical shift [14,15].

In daily practice, MDCT is used to follow up the GD patients presenting with TH. Typically, true thymic hyperplasia and lymphoid hyperplasia manifest as diffuse symmetric enlargement of the thymus; suggested lymphoid thymic hyperplasia may have higher HU MDCT attenuation values (i.e. >40) compared to true thymic hyperplasia [13,14]. True thymic hyperplasia includes rebound hyperplasia to chemotherapy/steroids, radiation therapy, burns, and other severe systemic stress. Lymphoid follicular thymic hyperplasia or autoimmune thymitis

includes myasthenia gravis, systemic lupus erythematosus, scleroderma and Grave's disease. MDCT attenuation of the thymus on contrast-enhanced MDCT is significantly higher in patients presenting with lymphoid hyperplasia than in patients with true hyperplasia, with an optimal cut-off value (lymphoid hyperplasia versus true hyperplasia) being greater than 41.2 HU.

Thanks to Thiamazole therapy, the thymic size and attenuation significantly reduced with a concomitant decrease in TRAb levels under the euthyroid state.

The presence of TSH receptors in the nonneoplastic human thymic tissue was clearly demonstrated by polymerase chain reaction amplification and immunohistochemistry [11] and again explains the physiopathogenesis of TH.

Regarding clinical symptoms assessment, chest discomfort, shortness of breath, upper chest pain are nonspecific but are classically reported in cases of thymic enlargement. They can be totally absent in Scappaticcia et al 's series [10] (absent in 20/20cases), or present in 9/13cases [6]. Clinically, our patient fully recovered after three months of therapy and is still disease free at three years follow-up.

Regarding TH size, TH disappears within twelve months of antithyroid drug therapy, with 60% of volume reduction at six months. This is consistent with our reported rate of 75% of volume reduction at nine months, and normalization at twelve months [10, 16] (Table 1).

Regarding other treatment issues, TH usually disappears within six months after thyroid gland surgery; and after I-131 therapy too, as reported by Jingui et al, [16]. The latter reported a correlation between the thymic size and serum level free-T3 decline after I-131 therapy [17].

Last but not least, overlooking the hyperthyroid status of patients presenting with thymic hypertrophy might lead to the development of stressful « acute thyroid storm » after thymectomy (acute change in mental status, fever, tachycardia, hypercapnic respiratory failure) [18].

Thus Haired et al proposed a management algorithm where MDCT plays a key role in diagnosis and follow- up of GD patients presenting with TH, in assessing volume and mediastinal mass attenuation, according to Murakami et al reports and thymic sizing charts [6,11]. In suspicious cases as in our report, MRI should be performed to state the decrease of signal on chemical shift weighted images, which reflects the typical fatty infiltration of TH, whereas anterior mediastinal tumors of the thymus lack fatty infiltration [14] (Table 1).

Moreover, typical homogeneous triangular shaped TH in a hyperthyroidism context indeed provides a high predictive value for suspicious cases of Grave's disease [10].

CONCLUSION

Thyrotoxicosis crisis may mimic acute pulmonary embolism. should be aware of the association of thymic hyperplasia in patients presenting with Graves' hyperthyroidism and its resolution with the reversibility of the hyperthyroid state to prevent unnecessary thymic surgery with its relevant risks.

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